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HOMOZYGOUS α6 INTEGRIN GENE MUTATION IN EPIDERMOLYSIS BULLOSA WITH CONGENITAL PYLORIC ATRESIA. Jouni Uitto, Virginia E. Kimonis, Yili Xu, Elena N. Spanou and Leena Pulkkinen. Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Philadelphia, PA; Department of Pediatrics, Southern Illinois University School of Medicine, Springfield, IL; The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus.

Junctional epidermolysis bullosa (JEB) is a heterogenous group of autosomal recessive skin diseases characterized by fragility of the dermal-epidermal junction. A distinct variant of non-lethal JEB is associated with congenital pyloric atresia (EB-PA). Previous immunofluorescence studies have suggested that the expression of the α6β4 integrin is altered in the skin of these patients. In this study, we have elucidated the molecular basis of EB-PA in a family with three affected individuals. We first determined the intron-exon organization of the α6β4 integrin genes, ITGA6 and ITGB4, and developed a mutation detection strategy using genomic DNA as template for PCR amplification of exons, followed by heteroduplex analysis and direct nucleotide sequencing. Examination of ITGB4 did not reveal any pathogenetic mutations. In contrast, analysis of ITGA6 disclosed that the affected individuals were homozygous for a G-to-T transversion in the first nucleotide of the intron downstream from a 161 bp exon. Direct sequencing of the parents' DNA revealed that they were heterozygous for this mutation, which could be verified by digestion with *Hph*I restriction enzyme. This mutation, 1856+1G→T, affected the 5' donor splice site (EXON-gt) predicting aberrant splicing of the 161-bp exon. This exon skipping is out-of-frame, potentially resulting in premature termination codon and absence of the α6 integrin subunit. Aberrant expression of the α6β4 integrin apparently explains the extreme fragility and blistering of the skin as a result of minor trauma.